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STEPHEN E REITER
PRETTY SCHROEDER BRUEGGEMANN AND CLARK
444 SOUTH FLOWER STREET
SUITE 2000
LOS ANGELES CA 90071

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on Paper 26 Jul 95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 30-53 are pending in the application.
   Of the above, claims 30-35, 41-50, 53 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 36-40, 51-52 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 30-53 have been presented for examination.

The preliminary amendment filed 26 July 1995 and unexecuted Declaration filed 21 August 1995 have been received and entered.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claim 30, drawn to *in vivo* modulation of lipid metabolism with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

II. Claims 31-35, drawn to *in vivo* modulation of non-malignant skin processes with 9-cis retinoic acid, classified, for example, in Class 514, subclass .

III. Claims 36-40 and 51-52, drawn to *in vivo* modulation of malignant cells with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

IV. Claims 41-42, drawn to *in vitro* modulation of cell differentiation with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

V. Claims 43-44, drawn to *in vitro* modulation of cell proliferation with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

VI. Claim 45, drawn to *in vitro* modulation of retinol binding protein with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

VII. Claim 46, drawn to *in vitro* modulation of limb morphogenesis with 9-cis-retinoic acid, classified, for example, in Class 514, subclass .

VIII. Claims 47-50 and 53, drawn to retinoic acid analogs and compositions, classified, for example, in Class , subclass .

The inventions are distinct, each from the other because of the following reasons:

Inventions Groups I-VII are each drawn to patentably distinct processes which can each be performed without the particulars of the other processes. Groups I-III are all *in vivo* processes, while Groups IV-VII are all *in vitro* processes. For Groups I-III, lipid metabolism (I) can be modulated without recourse to modulating malignant cells (III) or skin processes (II). Similarly malignant cell can be modulated without modulating skin processes. For Groups IV-VII each of the modulated processes is a distinct process. Cell differentiation (IV) can be modulated without proliferation (V) or effecting retinol binding protein (VI) or limb morphogenesis (VII). Each of the *in vitro* processes can be performed in the absence of the other groupings.

Inventions VIII and I-VII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the compounds and compositions are much broader than the active compound claimed in the processes. The disclosure indicates that other compounds within the scope of the claimed compounds of Group VIII are expected to be used in the claimed processes. Many of these processes are known to be modulated by compounds other than retinoids.

Because these inventions are distinct for the reasons given above and the Groups have acquired a separate status in the art as shown by their divergent subject matter and because separate searches of the non-classified literature would be required, restriction for examination purposes as indicated is proper.

During a telephone conversation between Attorney Stephen Reiter and examiner Jon P. Weber on 04 October 1995, a provisional election was made with traverse to prosecute the invention of Group III, claims 36-40 and 51-52. Affirmation of this election must be made by applicant in responding to this Office action. Claims 30-35, 41-50 and 53 are withdrawn from

further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Priority to USSN 07/809,980 is alleged in the supplemental amendment filed 26 July 1995. In support of this allegation, the unexecuted Declaration of Dr. Stein was filed on 21 August 1995. To obtain the benefit of an earlier filed U.S. application under 35 U.S.C. § 120, the priority document must disclose that portion of the invention that serves as the basis for the claim of priority in accordance with 35 U.S.C. § 112 by fully enabling the claims of the instant U.S. application.

In the first place, the instant parent application, PCT/US92/11214 is properly a continuation in part of US 07/809,980. The disclosure of 07/809,980 asserts at page 11 that "processes capable of being modulated by retinoid receptors ... include ... *in vivo* modulation of malignant cell development". This is the sole support for the claim invention which can be found in this application. This assertion is not further supported by evidence. Further the disclosure does not specifically set forth 9-cis-retinoic acid as the efficacious compound. The assertion at page 11, contrary to Dr. Stein's Declaration, does not teach a skilled artisan **at the time the invention was made** how to make and/or **use** the claimed process to treat malignancy. There is no evidence that the claimed process

had been tested *in vivo* or in a suitable *in vitro* model. There is no basis to assert that a skilled artisan at the time the invention was made would have immediately deduced that the claimed process could treat malignant cells. In a field as unpredictable as malignancy treatments, and where skepticism of claimed treatments is high, the claimed process cannot be said to have been enabled at the time of the alleged invention without solid evidence. Mere contemplation that some compounds might be useful in the treatment of cancer is not the same thing as reduction to practice.

As a consequence of the lack of enablement, priority to 07/809,980 will not be considered with respect to the claimed invention for the purposes of prior art determinations. A priority date of 18 December 1992, the filing date of PCT/US92/11214, will be considered the effective filing date. For a more thorough analysis of the enablement issue *vide infra*.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

An *in vivo* method of treating premalignant or precancerous epithelial lesions and malignant cell development by administration of 9-cis-retinoic acid is claimed.

The treatment of malignant cells by administration of 9-cis-retinoic acid is alleged at page 12 of the disclosure. Allegedly useful ranges for administration are set forth at page 26 of the disclosure. Exemplification in support of the alleged treatment is presented in examples 6 and 7 of the disclosure.

While it is not necessary in general for an application to provide explicit exemplification for an alleged claim, when there is reason to doubt the objective truth of the asserted claims, it is proper to reject the claims for lack of enablement. There are two main considerations: predictability and exemplification. That is, based on the evidence presented, would a skilled artisan have predicted that the claimed process would achieve the claimed outcome. Further, could the claimed process be practiced without undue experimentation?

It is ever the case with alleged *in vivo* treatments and especially in controversial areas such as treating malignancy, that claims for such treatment are treated with skepticism. The

disclosure as filed only provides an *in vitro* assay. The whole organism is more complicated than cell culture. Potential problems with administering a composition *in vivo* are legion. Some of these problems are uptake of the compound, targeting the effected tissue, effective dose ranges, clearance and tolerance.

The disclosure does not provide evidence that there is a nexus between the *in vitro* cell culture tests of examples 6 and 7 and the alleged treatment with 9-cis-retinoic acid in whole organism. In example 7 the all trans and 9-cis retinoic acid inhibit the growth of two tumor cell lines to the same degree. The mechanism of action is not clear from this example. In addition, it is said to be known in the art that all trans retinoic acid is used to prevent development of benign and malignant tumors. The implication is that by analogy the 9-cis-retinoic acid will also prevent development of benign and malignant tumors. This might be a credible nexus if both compounds acted by the same mechanism. However, much of the disclosure is dedicated to demonstrating that these two compounds have different sites and mechanisms of action (*vide infra*). The 9-cis compound is demonstrated to be highly specific for the RXR receptors over the RAR receptors as compared to the all trans compound.

According to Ex parte Forman et. al., 230 USPQ 546, determination of what constitutes undue experimentation in a

given case requires the application of standards of reasonableness, having due regard for nature of invention and state of art; the test is not merely quantitative, since considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to direction in which experimentation should proceed to enable determination of how to practice desired embodiment of invention claimed.

The factors to be considered in determining what constitutes undue experimentation have been summarized as: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims.

In the instant case, the examples are of several types. Some of the examples establish that 9-cis-retinoic acid is an endogenous ligand which binds to the RAR and RXR receptors with a specificity for RXR over RAR which is about forty-fold greater than all-trans retinoic acid. Other examples demonstrate that 9-cis retinoic acid transactivates genes containing an RXR activatable promoter. In example 6, 9-cis-retinoic acid was shown to inhibit HL60 cell differentiation to a greater degree than all trans retinoic acid. The effects of both ligands was potentiated

by alpha-interferon. In example 7, 9-cis-retinoic acid inhibited the growth of a murine melanoma cell line and a human primary metastatic cell line in a concentration dependent manner which was nearly the same as for all trans retinoic acid.

None of the examples addresses the problems associated with *in vivo* treatments discussed above. Further, there is no evidence of record which provides a clear basis for the alleged effective dosages of 9-cis retinoic acid in the claimed process as set forth at page 26 of the disclosure. Each treatment process would presumably require a different mode of application and dosage levels. No clear guidance is provided on the selection of application method or dosage rate for the claimed process. Given the considerable unknowns and the potent effects of 9-cis-retinoic acid on a variety of systems, a skilled artisan would not be able to predict the outcome of treatment with 9-cis-retinoic acid or what dosages would be effective. In addition given the limited disclosure in a highly unpredictable art, a skilled artisan would not expect to have a reasonable likelihood of success in following the claimed process. As a consequence the claims are not enabled for the claimed process of preventing malignant cell development *in vivo* or treating precancerous or premalignant epithelial lesions *in vivo*.

Claims 36-40 and 51-52 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 36-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites "modulation" which is vague and indefinite because the nature and manner of the "modulation" is unclear. In particular modulation could be inhibition or enhancement. It is not clear why enhancement of malignant cell development would be considered an effective therapy. The definition for modulate provided at pages 7-8 of the disclosure applies to inducing and repressing genes and does not appear to be applicable to the broader "cell development" claimed.

Claim 38 recites an improper Markush group. The proper format is "selected from the group consisting of A, B, and C".

The following rejections are based upon the determination that priority to 07/809,980 is not being accorded for the purposes of prior art considerations.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

An *in vivo* method of treating premalignant or precancerous epithelial lesions and malignant cell development by administration of 9-cis-retinoic acid is claimed.

Claims are 36, 38-40 and 51-52 are rejected under 35 U.S.C. § 102(a) as being anticipated by Toyada et al. (JP-'076) or Toyoda et al. (JP-'058).

Toyada et al. (JP-'076) and Toyoda et al. (JP-'058) both disclose that 9-cis-retinoic acid can be used as an antitumor agent and ulcer therapuetic for skin and digestive tract.

Claims are 36 and 38-40 are rejected under 35 U.S.C. § 102(a) as being anticipated by Matsushima et al. (1992).

Matsushima et al. (1992) disclose that 9-cis-retinoic acid induces human promyelocytic HL-60 cell differentiation activity by binding to both RARs and RXRs.

Claims 36 and 38-40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yen et al. (1986).

Yen et al. (1986) disclose that 9-cis-retinoic acid induces both phenotypic differentiation and G1/0 specific growth arrest in human promyelocytic HL-60 cells.

Claims 36-40 and 51-52 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Bollag et al. ('071).

Bollag et al. ('071) present claims and disclosure are nearly identical to the instant claims which is apparent because of the stated intent of the instant application to initiate an interference with Bollag et al. ('071).

Bollag et al. ('071) further disclose at column 3, lines 38-46 that treatment of precancerous lesions and malignant tumors of epithelial nature can be effected with 9-cis-retinoic acid in combination with biological response modifiers such as interferons.

No claims are allowed.

Any inquiry concerning this communication should be directed to Jon P. Weber, Ph.D. at telephone number (703) 308-4015. The examiner can normally be reached during the hours of 06:30 to 16:30 Eastern (off first Friday).

If attempts to reach the examiner by telephone are unsuccessful, a message may be left on the voice mail. The fax number for Art Unit 1808 is (703) 308-0294. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J.P.W. 17 October 1995

MICHAEL G. WITYSHYN
SUPERVISORY PATENT EXAMINER
GROUP 1800

10-28